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Ventricular function and vascular dimensions after Norwood and hybrid palliation of hypoplastic left heart syndrome

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ABSTRACT

Objective: Norwood and hybrid procedure are two options available for initial palliation of patients with hypoplastic left heart syndrome (HLHS). Our study aimed to assess potential differences in right ventricular (RV) function and pulmonary artery dimensions using cardiac magnetic resonance (CMR) in HLHS survivors.

Methods: 42 Norwood (mean age 2.4±0.8) and 44 hybrid (mean age 2.0±1.0 years) patients were evaluated by CMR after stage II palliation prior to planned Fontan completion. Initial stage I Norwood procedure was performed using a modified Blalock-Taussig shunt while the hybrid procedure consisted of bilateral pulmonary artery banding and arterial duct stenting. Need for reinterventions and subsequent ouctomes were also assessed.

Results: Norwood patients had larger RV end-diastolic dimensions (91±23 vs 80±31 ml/m^2, p=0.004) and lower heart rate (90±15 vs 102±13, p<0.001) than hybrid patients. Both Norwood and hybrid patients showed preserved global RV pump function (59±9 vs 59±10 %, p=0.91) while RV strain, strain rate and intra-ventricular synchrony were superior in the Norwood group. Pulmonary artery size was reduced (lower lobe index 135 ± 81 vs 161 ± 70 mm^2/m^2, p=0.02) and reintervention rate was significantly higher in the hybrid group whereas subsequent outcome did not differ significantly (p=0.24).

Conclusions: Norwood and hybrid strategy were associated with equivalent and preserved global RV pump function while development of the pulmonary arteries and reintervention rate were superior using the Norwood approach. Impaired RV myocardial deformation as a potential marker of early RV dysfunction in the hybrid group may have a negative long-term impact in this population.

KEY QUESTIONS:

What is already known about this subject?

Compared to the Norwood approach, initial stage I palliation using the hybrid procedure may preserve RV function but also carries a higher risk of pulmonary arterial compromise. However, data about the effects of Norwood and hybrid procedure on RV function and vascular development in 'standard risk' HLHS patients are limited.

What does this study add?

Our study demonstrated that both Norwood and hybrid strategy were associated with preserved global RV pump function prior to Fontan completion while growth of the pulmonary arteries and reintervention rate were superior using the Norwood approach. Reduced RV myocardial deformation in the hybrid group may indicate early RV dysfunction.

How might this impact on clinical practice?

Stage I hybrid palliation strategy for 'standard risk' HLHS patients was associated with preserved global RV function but reduced indices of RV myocardial performance. Advantageous pulmonary artery development and less reinterventions therefore suggest favourable effects using the Norwood approach.

INTRODUCTION

Although initially considered as an alternative therapy in 'high risk' neonates,[1] some institutions have succeeded in adopting the hybrid procedure as the primary stage I palliation for all hypoplastic left heart syndrome (HLHS) patients.[2, 3, 4] Thy hybrid procedure includes bilateral pulmonary artery banding, stenting of the arterial duct and atrial septostomy in case of a restrictive interatrial communication.[5] In theory, the potential benefits of the hybrid strategy arise from the avoidance of early cardiopulmonary bypass in the first days of life thereby avoiding ischemic insult to the neonatal heart, brain and other organs. This may preserve right ventricular (RV) myocardial function in the long-term thereby leading to advantageous transplant-free survival. However, data comparing the hybrid strategy with the Norwood approach (modified Blalock-Taussig shunt) and/or the right ventricle-pulmonary artery conduit (Sano shunt) included either smaller groups of patients at one single institution [6, 7, 8, 9] or were obtained from larger national registries that only allow limited conclusions mainly due to substantial bias in patient selection and technical modifications varying among centres.[10, 11, 12]

Our study aimed to assess potential differences in RV remodeling, reintervention rates and subsequent outcome of 'standard risk' HLHS patients who initially underwent the Norwood or the hybrid approach as the first-line stage I palliation strategy. Therefore, HLHS patients after stage II palliation from two european centres were evaluated using cardiac magnetic resonance (CMR) imaging to assess RV size, function and pulmonary artery dimensions as prior to planned Fontan completion.

MATERIALS AND METHODS

Study population and design

Ethical and institutional approval was obtained. Patients with HLHS who underwent a CMR study as part of their routine clinical preoperative assessment prior to Fontan completion with creation of a total cavopulmonary connection (TCPC) at Evelina London Children's Hospital, United Kingdom (between 2008 and 2014) and the Pediatric Heart Centre, Giessen, Germany (between 2008 and 2015) were included after identification by the departmental databases. HLHS was defined as any combination of mitral stenosis or atresia with aortic stenosis or atresia where the left ventricle was not felt adequate at that point to support the systemic circulation.

At Evelina London all patients with HLHS undergo a classical Norwood procedure unless they are high risk (<2.5kg, post-natal collapse with multi-organ dysfunction, intact or highly restrictive atrial septum, significant RV dysfunction, significant tricuspid regurgitation).[13] If patients are high risk, only then they are selected for the hybrid procedure. For this reason, only patients undergoing the primary Norwood Procedure at Evelina London were included. In Giessen, all patients undergo the hybrid procedure and are not pre-selected, and so the hybrid patients were taken from this institution. Patients were excluded if clinical data and/or CMR studies were incomplete or of poor image quality. Clinical data were retrospectively obtained from hospital medical records. Standard two-dimensional echocardiographic images were analysed and tricuspid valve regurgitation was qualitatively graded as: °I=trivial/mild, °II=moderate and °III=severe. The review study protocol was approved by the local review boards of each institution.

Hybrid Stage I - III

Details of the Giessen hybrid approach have recently been published in detail.[14] Briefly, the stage I approach consists of surgical bilateral pulmonary artery banding (bPAB), stenting of the arterial duct (PDA) and atrial septostomy within the first 10 postnatal days (**Figure 1**). At the age of 4-6 months, a comprehensive stage II operation is performed and includes aortic arch reconstruction, balloon dilatation and/or patch augmentation at sites of the PAB, atrioseptectomy and a bidirectional Glenn anastomosis. Stage III surgery is then completed by a TCPC typically performed at the age of 3-4 years using an extracardiac conduit placed between the vena cava inferior and the right pulmonary.[14]

Norwood Stage I - III

The Norwood stage I procedure at Evelina London consists of a size appropriate modified BTS (3.0/3.5/4.0 mm), atrioseptectomy with reconstruction of the aortic arch (**Figure 1**). Stage II is performed at 3-6 months of age as a hemi-Fontan with further stage III completion at 3-4 years of age with a lateral tunnel TCPC. While any stenosis in the right pulmonary artery is included in the hemi-Fontan operation, surgical intervention on the left pulmonary artery is avoided whenever possible.

Cardiovascular magnetic resonance (CMR) acquisition and analysis

With the exception of anaesthetic strategy, the CMR protocols at the two institutions were comparable and consisted of, amongst others, standard cine volumetric assessment of the single ventricle and contrast-enhanced angiographic assessment of the vasculature.

CMR studies were performed on a 3-T system (Verio, Siemens, Erlangen, Germany) in hybrid and a 1.5-T scanner (Achieva, Philips Healthcare, Best, the Netherlands) in Norwood patients. Sedation using a combination of midazolam and propofol was applied in hybrid patients whereas the Norwood patients underwent general anaesthesia employing inhaled sevofluorane and a low-dose remifentanyl infusion. A stack of short-axis slices from the base of the heart to the apex was used for quantification of RV volumes using gradient echo cine (GRE) sequences in free-breathing technique in the hybrid and a steady-state free precession (SSFP) cine sequence with short cessation of ventilation for the duration of each acquisition in the Norwood group. Sequence parameters were as follows (hybrid and Norwood, respectively): TR 56/3.6 ms, TE 2.5/1.8 ms, flip angle 12°/60°, slice thickness 5/4-6 mm, in plane image resolution 1.4x1.4x5.0/1.3x2.0x4-6 mm. A 3-dimensional (3D) contrast-enhanced magnetic resonance angiographic (CE-MRA) scan was obtained in the coronal plane, using gadopentetate dimeglumine (Magnevist, Bayer, Leverkusen, Germany or Magnevist, Berlex Laboratories, Wayne, New Jersey) at a dose of 0.1-0.2 mmol/kg using the following parameters: slice thickness 1.2-1.4/1.2-1.7 mm, flip angle 19°/40°, generalized autocalibrating partially parallel acquisition imaging, with an acceleration factor of 2.

Volumetry and vessel measurements

End-diastolic and end-systolic volumes, stroke volumes and ejection fractions for the RV and LV (where present LV) were calculated by dedicated software (ARGUS, Siemens, Erlangen, Germany and Viewforum EWS Version 2.0, Philips Healthcare, Best, the Netherlands).[15]
User-defined multiplanar reformatted (MPR) images were obtained using dedicated software (OsiriX Viewer). The indexed lower lobe index (LLI) was used for evaluation of pulmonary artery size and was calculated as the sum of the cross-sectional areas of the lower lobe branch of the right and left pulmonary arteries. Aortic dimensions were measured at predefined levels as displayed in **Figure 2A**. All parameters were indexed to body surface area (BSA).

CMR feature tracking for the assessment of myocardial strain, strain rate and synchrony

CMR feature tracking (CMR-FT) allows quantitative assessment of myocardial strain derived from standard short axis and 4-chamber cine CMR images using CMR-FT software (TomTec Imaging Systems, Unterschleissheim, Germany). The values of global peak strain and strain rate were recorded and intraventricular synchrony was assessed from the time to peak analysis as the maximum wall delay between the 6 segments as well as the standard deviation of the 6 segments (**Figure 2B**). RV diastolic function was derived from the global circumferential strain rate curve with determination of the early diastolic strain rate wave.

Statistical analysis

All continuous variables were tested for normality using the Kolmogorov-Smirnov test and are presented as mean with standard deviation. Comparisons between the Norwood and the hybrid group were made with the Student t-test, the Mann-Whitney U test or the Fisher's exact test, as appropriate. Pearson's correlation coefficient was used to analyse simple linear relationships between different variables. Kaplan–Meier survival analysis was conducted with definition of end point as the composite of all-cause mortality and heart transplantation. Analysis was performed using GraphPad statistical software package (San Diego, California, USA). A p value ≤ 0.05 was considered statistically significant. The intra- and interobserver variability for single RV strain and synchrony measurements were assessed using the coefficient of variation (CV, defined as the standard deviation of the differences divided by the mean).

RESULTS

Patient characteristics and clinical findings

The study consisted of 44 hybrid patients (mean age 2.0 ± 1.0 years, 14 females) and 42 Norwood patients (mean age 2.4 ± 0.8 years, p=0.08, 15 females). Both groups were age and sex matched. There was no difference in the underlying HLHS subtype diagnosis, frequency of antenatal diagnosis, preterm birth, birth weight and severity of tricuspid valve regurgitation **Table 1**).

Reinterventions

A significant higher rate of reinterventions due to pulmonary artery stenosis after stage II was necessary in the hybrid group (19 (43%) vs 1 (2%), p=0.0003) (**Table 2**). Reinterventions after stage I due to obstruction of the stented arterial duct/inadequate tightness of the PAB (hybrid) or surgical revision of the BT-shunt (Norwood) were also higher in the hybrid group (11 (25%) vs 1 (2%), p=0.04) and repeated atrial septostomy was performed in 13 (30%) hybrid and in 1 (2%) Norwood patients (p=0.0008).

Volumetry

Norwood patients had significantly higher RV end-diastolic (91.2 ± 23.0 vs 80.9 ± 31.7 ml/m^2; p=0.004) and similar end-systolic volumes (38.1 ± 16.5 vs 34.8 ± 22.9 ml/m^2, p=0.07) (**Figure 3**). Due to a significantly higher heart rate in the hybrid group (102 ± 13 vs 90 ± 15 beats per minute; p<0.001) cardiac output was almost similar in the two groups (4.9 ± 1.2 vs 4.7 ± 1.2 l/min/m^2, p=0.44) RV ejection fraction (EF) was preserved in both groups and showed no significant difference (59.4 ± 10.3 vs 59.2 ± 9.0 %, p=0.91) **(Table 3**).

Feature tracking analysis including synchrony measurements

Norwood patients showed significant more negative RV longitudinal (LS) (-16.5 ± 5.5 vs -

13.2 ± 5.9 %, p=0.008), circumferential (CS) (-18.4 ± 5.6 vs -14.7 ± 5.6 %; p=0.001), and radial strain (RS) values (21.5 ± 9.5 vs 13.9 ± 8.7 %; p=0.0002) than hybrid patients (**Table 3 and Figure 3**). Systolic longitudinal strain rate (LSR -1.25 ± 0.60 vs -1.05 ± 0.47 1/s, p=0.027) and radial strain rate (RSR 1.17 ± 0.40 vs 1.03 ± 0.37 1/s, p=0.05) values were also higher in the Norwood group. Early diastolic circumferential strain rate showed no significant difference between the two groups (1.5 ± 0.7 vs 1.3 ± 0.5 1/s, p=0.09). RV circumferential and radial intra-ventricular synchrony was found to be significantly lower in the hybrid group.

Heart rate was significantly related to RV-LS (r=0.27, p=0.01) and RV–CS (r=0.31, p=0.004). Indexed RV stroke volume showed significant correlations with RV-CS (r=0.34, p=0.0014) and RV–RS (r=0.39, p=0.0003).

CMR-Angiography for evaluation of pulmonary artery and aortic dimensions

Measurement of the lower lobe index (LLI) was possible in 30 patients (68%) in the hybrid group (analysis was not possible in 14 patients due to stent artefacts) and in 39 patients (93%) in the Norwood group. While right LLI did not reach a statistical significant difference (82 ± 50 vs 93 ± 79 mm^2/m^2; p=0.08) the left LLI was significantly decreased in the hybrid group (55 ± 31 vs 70 ± 45 mm^2/m^2; p=0.037) resulting in a lower total LLI in this group (135 ± 81 vs 161 ± 70 mm^2/m^2; p=0.021) (**Figure 2A** and **Table 4**).

No differences in aortic dimensions were found and there was no evidence of aortic arch obstruction or relevant coarctation in any patient (**Table 4)**.

Further palliation and outcome

In the Norwood group, one patient died between stage II and III due to severe airway issues while the remaining 41 patients underwent stage III (**Figure 1**). Two of these patients died in the postoperative period (one from ultimate bowel perforation and the other from overwhelming sepsis). Of the 44 hybrid patients, three patients underwent cardiac transplantation due to severe RV dysfunction prior to stage III. Thirty-five patients have undergone stage III. One patient died during the postoperative period due to pulmonary thromboembolic complications with the need for extracorporeal membrane oxygenation. The mean follow-up interval after stage III was significantly longer in the Norwood group (3.7 ± 1.4 years) than in the hybrid group (2.0 ± 2.1 years; p<0.0001) with no further adverse events in both groups. Kaplan-Meier survival analysis (**Figure 4**) showed no statistical difference in mid-term outcome between the two groups (p=0.24).

DISCUSSION

Our study assessed the pattern of RV remodeling, development of the pulmonary arteries, reinterventions and outcome in HLHS-patients prior to planned Fontan surgery who were initially palliated either by Norwood or hybrid strategy. Importantly, these approaches were used as the first-line therapy in ‘standard risk’ HLHS-patients in the respective centre. While global RV pump function was found to be preserved in both groups, hybrid patients showed lower RV strain and strain rate values, smaller pulmonary arteries and a more reinterventions than Norwood patients whereas subsequent outcomes did not differ significantly.

Single right ventricular size and function

Preservation of single RV function represents a key factor during staged palliation of children with HLHS.[16] Recent single-institution studies assessed RV function qualitatively and demonstrated a profound impact of ventricular dysfunction on atrioventricular valve competence and transplant-free survival while initial Norwood or hybrid strategy seemed to be unrelated to the presence of RV impairment. [6, 7] A further study by Grotenhuis and colleagues assessed RV properties by echocardiography in HLHS-patients throughout different stages of palliation [17] which found only minor differences in some indices of RV function leading to the conclusion that the used surgical strategy may not have a decisive effect on intrinsic myocardial and tricuspid valve function.

By quantifying RV function with CMR, our study found equivalent and preserved ejection fraction in both groups creating optimal preconditions for further Fontan completion. However, reduced systolic RV strain and strain rate values as well as a higher degree of intraventricular dysynchrony are indicative of subclinical myocardial dysfunction and unfavourable remodeling in hybrid patients. While in both strategies the myocardium is subjected to volume loading and likely ischemia prior to stage II, the mechanisms and time points of myocardial insult differ.[7] The hybrid strategy shifts the risks of major open-heart surgery from the neonatal period to an older age, which may be beneficial given the known vulnerability of neonatal myocardium to ischemia caused by cardiopulmonary bypass. However, the risks of the hybrid procedure include impaired myocardial blood supply due to retrograde perfusion of the hypoplastic aortic arch and ascending aorta.[18, 19] Although survival analysis showed no statistical significance, the evolution of severe RV dysfunction in three patients in the hybrid group with subsequent need for cardiac transplantation support this hypothesis. Importantly, unlike the Sano strategy, both classical Norwood and hybrid strategies avoid a ventriculotomy thereby preventing potential irrerversible myocardial injury.[16, 20, 21]

The observed variations in heart rate, volumes, strain and synchrony measurements, must also be interpreted with regards to the different anaesthetic strategies used which are known to have substantial hemodynamic effects. The observed heart rate and stroke volume dependency of the strain values clearly support this suggestion. In contrast, RV strain rate is known to be a more load-independent parameter of RV function in HLHS-patients as recently shown in an invasive conductance-catheter study.[22] The lower systolic strain rate values in the hybrid group therefore reflects impaired intrinsic RV myocardial performance that cannot be explained by altered loading conditions due to anaesthesia.

Reinterventions

A number of studies have already shown that pulmonary artery stenosis occurs frequently in HLHS patients undergoing the hybrid procedure.[14, 23, 24] This can be explained by the previous banding of the pulmonary arteries and their subsequent need for surgical reconstruction at comprehensive stage II. Although branch pulmonary artery stenosis and distorsion has also been reported using the Norwood approach, our results confirm previous observations that revealed a higher pulmonary artery reintervention rate associated with the hybrid procedure. [6, 23] Importantly, the need for reinterventions after hybrid stage I was significantly higher, mainly due to obstruction of the stented arterial duct and repeated percutaneous atrial septostomy to guarantee an unobstructed interatrial communication. In addition to the well-known risks associated with any transcatheter intervention, such multiple catheterization procedures will lead to a higher radiation burden over lifetime.

Pulmonary artery and aortic size

By assessing the lower lobe index as a measure of central pulmonary artery growth, Norwood patients showed superior development of their pulmonary arteries. This finding is in accordance with previous reports [6, 25] and suggests that even in the absence of significant branch pulmonary artery stenosis, pulmonary artery development is affected by previous restriction of pulmonary blood flow by bilateral PA banding. Considering that patients with prior stents were not included in the analysis due to imaging artefacts, the difference in pulmonary artery size between the two groups is probably even more distinct. It must also be taken into account that the surgical techniques to create a superior cavopulmonary connection differed between the two groups which potentially leads to variable pulmonary arterial distortion during growth. No significant difference was seen in the short term after TCPC, but given the importance of adequate branch pulmonary artery size in the Fontan circulation, longer-term differences need to be assessed.

Despite preceding stent implantation in the arterial duct, quality of aortic arch reconstruction following comprehensive stage II was achievable with a low reintervention rate in the hybrid group. Furthermore, aortic dimensions measured at different levels showed equivalent sizes suggesting that both strategies prepare adequate aortic architecture at pre-Fontan stage.

Study limitations

Quantification of ventricular volumes by CMR cine imaging is influenced by the used the type of sequence. SSFP imaging overestimates ventricular volumes compared to GRE sequences [26, 27, 28] suggesting that differences in RV volume may also be due to the choice of imaging protocols rather than treatment methodology. Ventricular function (i.e. ejection fraction), however, is affected only in a minor way by the applied sequence [27, 28, 29].

The retrospective and non-randomized nature of this study resulted in a bias in patient selection and therefore limits further interpretation of the presented data. In particular, differences in early mortality and morbidity between the groups prior to stage II may thus be missed and may affect the results.[13] [14] Importantly, although hybrid patients were not pre-selected in their institution, risk-profiles between the two groups were comparable.

The dual-centre design may also impose a bias as some of the differences detected between the groups may be more related to individual institutional practice rather than representing a real effect of the procedure. Although the two groups were well matched, differences in age (for example earlier stage II volume unloading surgery in the hybrid group) and type of surgical procedures, management protocols, drug therapy as well as indication and type of reintervention could have influenced the results.

CONCLUSIONS

Norwood and hybrid strategy as initial palliation of ‘standard risk’ HLHS patients were associated with equivalent and preserved global RV pump function while development of the pulmonary arteries and reintervention rate were superior using the Norwood approach. Impaired RV myocardial deformation as a potential marker of early RV dysfunction in the hybrid group may have a long-term negative impact in this population.

Table legends

Table 1

Demographic data of the study population

Variable	Hybrid	Norwood	Significance (*p*-value)
Patients, n	44	42	
Male/Female	30/14	27/15	0.82
Body weight, kg	11.5 ± 3.2	12.3 ± 3.3	0.15
BSA (m^2)	0.52 ± 0.11	0.55 ± 0.07	0.14
Age at study, years	2.0 ± 1.0	2.4 ± 0.8	0.08
<u>Diagnosis</u>			
Hypoplastic left heart syndrome			0.88
Mitral atresia/aortic atresia	22	21	
Mitral atresia/aortic stenosis	2	2	
Mitral stenosis/aortic atresia	10	7	
Mitral stenosis/aortic stenosis	10	12	
Age at stage I, days	4.0 (1 - 47)	4.0 (1 – 66	0.11
Age at stage II, months	4.2 ± 1.6	5.4 ± 1.7	**<0.001**
Follow-up since stage II, months	19.8 ± 12.7	24.3 ± 8.7	0.06
Antenatal diagnosis, n (%)	32 (73)	33 (79)	0.62
Preterm (<37 week gestation), n	2	2	1.0
Birth weight, g	3188 ± 738	3100 ± 401	0.41
Transcutaneous oxygen saturation, %	84.1 ± 4.1	82.2 ± 3.9	0.16

Tricuspid valve regurgitation, °I/°II/°III, n	36/7/1	36/5/1	0.87

BSA, body surface area, *MA*, mitral atresia; *MS*, mitral stenosis; *AA*, aortic atresia; *AS*, aortic stenosis; data are presented as mean and 1 standard deviation.

Table 2

Reinterventions in the two study groups

Variable	**Hybrid n=44**	**Norwood n=42**	**Significance (*p*-value)**
Pulmonary artery interventions (after stage II)			
BAP, n (%)	5 (11)	0 (0)	**0.05**
Stent, n (%)	14 (32)	1 (2)	**0.0003**
Collateral coil occlusion (after stage II), n (%)	6 (14)	2 (5)	0.27
Coarctation dilation/stent (after stage II), n (%)	2 (5)	0 (0)	0.49
Reintervention PDA/PAB or BTS (after stage I), n (%)	11 (25)	3 (8)	**0.04**
ASD intervention (after stage I), n (%)	13 (30)	1 (2)	**0.0008**
TV repair (after stage II), n (%)	1 (3)	1 (2)	1.0

BAP, balloon angioplasty; *PDA,* persistent ductus arteriosus; *PAB,* pulmonary artery banding; *BTS*, modified Blalock-Taussig shunt; *ASD,* atrial septal defect; *TV,* tricuspid valve.

Table 3

Results of the CMR study and the feature tracking (FT) analysis including synchrony measurements

Variable	Hybrid n=44	Norwood n=42	Significance (*p*-value)
CMR			
HR, /min	102 ± 13	90 ± 15	**<0.001**
EDVi, ml/m^2	80.9 ± 31.7	91.2 ± 23.0	**0.004**
ESVi, ml/m^2	34.8 ± 22.9	38.1 ± 16.5	0.07
SVi, ml/m^2	46.0 ± 11.9	53.1 ± 12.4	**0.002**
EF, %	59.2 ± 9.0	59.4 ± 10.3	0.91
CI, l/min/m^2	4.7 ± 1.2	4.8 ± 1.2	0.44
CMR-FT			
LS, %	-13.2 ± 5.9	-16.5 ± 5.5	**0.008**
LSR, 1/s	-1.05 ± 0.47	-1.25 ± 0.60	**0.027**
CS, %	-14.7 ± 5.6	-18.4 ± 5.6	**0.001**
CSR, 1/s	-1.11 ± 0.44	-1.17 ± 0.36	0.41
RS, %	13.9 ± 8.7	21.5 ± 9.5	**0.0002**
RSR, 1/s	1.03 ± 0.37	1.17 ± 0.40	**0.05**
Early diastolic CSR, 1/s	1.3 ± 0.5	1.5 ± 0.7	0.09
Intraventricular synchrony			
LS			
Maximum wall delay (ms)	176 ± 114	154 ± 80	0.39

SD (time to peak) (ms)	93 ± 42	83 ± 37	0.25
CS			
Maximum wall delay (ms)	246 ± 131	133 ± 66	**<0.001**
SD (time to peak) (ms)	96 ± 56	51 ± 23	**<0.0001**
RS			
Maximum wall delay (ms)	256 ± 150	140 ± 106	**<0.0001**
SD (time to peak) (ms)	99 ± 60	58 ± 47	**0.0002**

EDV, enddiastolic volume; *ESV,* endsystolic volume; *SV,* stroke volume; *EF,* ejection fraction; *FT,* feature tracking; *LS,* longitudinal strain; *LSR,* longitudinal strain rate; *CS,* circumferential strain; *CSR,* circumferential strain rate; *RS,* radial strain; *RSR,* radial strain rate; data are presented as mean ± 1 standard deviation (SD).

Table 4

Results of the angiographic size of the pulmonary arteries and the aorta at predefined levels

Variable	Hybrid n=44	Norwood n=42	Significance (*p*-value)
CMR angiography			
Right LLI, mm^2/m^2	82 ± 50	93 ± 78	0.09
Left LLI, mm^2/m^2	55 ± 31	70 ± 35	**0.037**
LLI total, mm^2/m^2	135 ± 81	161 ± 70	**0.021**
Native aorta, mm^2/m^2	92 ± 103	93 ± 78	0.30
Neo aorta, mm^2/m^2	656 ± 183	658 ± 187	0.96
Ascending aorta, mm^2/m^2	595 ± 236	555 ± 184	0.38
Transverse arch, mm^2/m^2	476 ± 285	361 ± 151	0.13
Isthmus, mm^2/m^2	116 ± 60	136 ± 42	0.16
Descending aorta, mm^2/m^2	103 ± 50	100 ± 28	0.59
APC, n (%)	8 (18)	8 (20)	1.0

LLI, lower lobe index; *APC,* aortopulmonary collaterals; data are presented as mean ± 1 standard deviation.

Figure legends

Figure 1

Flow diagram displaying the various types of procedures, time points and clinical outcomes for HLHS palliation in the Giessen hybrid group and the London Norwood group.

HLHS, hypoplastic left heart syndrome; *PA*, pulmonary artery; *mBT*, modified Blalock-Taussig shunt; *PDA*, persistent arterial ductus arteriosus; *CMR*, cardiac magnetic resonance; *n*, number of patients; *HTx*, cardiac transplantation

Figure 2

Cardiac magnetic resonance (CMR) study

A Multiplanar reformatted (MPR) images of the branch pulmonary arteries (*left*) and the reconstructed aortic arch (*right*) from contrast-enhanced magnetic resonance angiography were used for assessment of the cross sectional areas right and left lower lobe index and aortic dimensions at predefined levels: 1. neo and native aortic root, 2. ascending aorta, 3. transverse arch after origin of the left common carotid artery, 4. aortic isthmus, 5. descending aorta.

B Feature tracking (FT) analysis of the single RV in the midpapillary short-axis view (for the assessment of circumferential and radial strain; upper panel) and in the '4-chamber view' (for the assessment of longitudinal strain; lower panel). After manually placing points along the ventricular endocardium in a single frame, the software algorithm follows this border throughout the cardiac cycle automatically and calculates strain/strain rate versus time for each of 6 segments.

Figure 3

Box-and-whiskers plots for the key variables of the CMR study. The central line represents the median with the boxes representing the 1st and 99th percentiles.

HR, heart rate; *RV*, right ventricle; *EF*, ejection fraction; *LS*, longitudinal strain; *CS*, circumferential strain; *LSR*, longitudinal strain rate.

Figure 4

Kaplan–Meier survival curves of the hybrid (blue line) and Norwood (orange line) group for the composite endpoint that consisted of all-cause mortality and heart transplantation (p=0.24). Displayed on the x-axis is the time (months) that has passed since the cardiac magnetic resonance (CMR) study prior to Fontan completion.

Online Supplement

Intra- and interobserver variability of single right ventricular global strain and synchrony measurements. One investigator blinded to the clinical and all other CMR data (P.H.) performed the feature-tracking analysis and after an interval of 12 weeks, both this observer and a second experienced observer (H.L.) repeated the feature-tracking analysis on the same images of 20 randomly selected subjects (10 Norwood and 10 hybrid patients). An appropriate analysis of the single RV using CMR-FT was feasible in all HLHS patients. Among all strain and synchrony parameters, global radial strain and radial synchrony showed the poorest reproducibility.

Variable	Intraobserver CV (%)	Interobserver CV (%)
Longitudinal strain (LS)	3.0	4.5
Circumferential strain (CS)	4.9	7.3
Radial strain (RS)	8.4	15.7
Early diastolic strain rate	3.2	4.9
LS SD time to peak	5.4	8.4
CS SD time to peak	8.2	12.5
RS SD time to peak	9.9	16.7

CV, coefficient of variation; *SD*, standard deviation.

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Conflict of interest

The authors declare that they have no conflict of interest.

Contributorship statement

HL, HB, TH, CA, CY, DS and GG have contributed to the conception and design of the study.

HL, MN, JW, PH, CS, CA, DA, RR and HA have contributed to the acquisition of data, analysis and interpretation of the data.

HL, JB, TH, DS and GG have contributed to the drafting of the article and have revised it critically for important intellectual content.

Statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a

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